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10/807,934	03/24/2004	Jason R. Fink	58211US004	5151

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3M INNOVATIVE PROPERTIES COMPANY
PO BOX 33427
ST. PAUL, MN 55133-3427

EXAMINER	
WOODWARD, CHERIE MICHELLE	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 06/28/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/807,934	FINK ET AL.	
	Examiner	Art Unit	
	Cherie M. Woodward	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 April 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-21* is/are pending in the application.

4a) Of the above claim(s) *3,4 and 8-21* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 5-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/28/05,11/22/04*
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Attachements Con't: 3. IDS: 12/30/04, and 08/18/04

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group 1, claims 1-2 and 5-7 in the reply filed on 28 April 2006 is acknowledged. The requirement is still deemed proper and is therefore made FINAL.

Formal Matters

2. Claims 1-21 are pending. Claims 3-4 and 8-21 are withdrawn as being drawn to non-elected inventions. Claims 1-2 and 5-7 are under examination.

Information Disclosure Statement

3. The information disclosure statements (IDS) submitted on 28 November 2005, 22 November 2004, 30 December 2004, and 18 August 2004, have been considered. Signed copies are attached. The reference line through in the 18 August 2004 IDS fails to comply with 37 CFR 1.98(a)(2), which requires a legible copy in English of each cited foreign patent document; each non-patent literature publication or that portion which caused it to be listed; and all other information or that portion which caused it to be listed. The reference will be considered when an English translation is supplied.

Provisional Obviousness-Type Double Patenting

4. Claims 1-2 and 5-6 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1, 2, 9 and 22 of copending Application No. 10/788731. Although the conflicting claims are not identical, they are not patentably distinct from each other because they are drawn to the same subject matter, render, and are rendered obvious by the instant claims.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d

887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Claim Rejections - 35 USC § 112, First Paragraph

Scope of Enablement

5. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

6. Claims 1-2, and 4-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a compound that selectively modulates at least one cellular activity mediated by human TLR7, does not reasonably provide enablement for a method of identifying a compound that selectively modulates at least one cellular activity from other TLRs from human or other species. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability, 5) existence of working samples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The claims recite a method of identifying a compound that selectively modulates at least one cellular activity of a plurality of cellular activities mediated by a common TLR comprising detecting modulation of a first cellular activity mediated by a TLR, detecting modulation of a second cellular activity mediated by the TLR and identifying the test compound as a compound that selectively modulates at least one cellular activity of a plurality of cellular activities mediated by a common TLR if the test compound modulates the first cellular activity to a different extent than it modulates the second cellular activity; wherein the test compound modulates the first cellular activity and does not modulate the second cellular activity; the method comprising selecting a target modulation profile of cellular activities mediated by a common TLR, determining the modulation profile of cellular activities mediated by a common TLR for a test compound and identifying the test compound as a target compound if the modulation profile of the test compound conforms to the target modulation profile; wherein the target modulation profile includes one or more TLR-mediated cellular activities that are not detectably modulated by a target compound; wherein the determining the modulation profile of a test compound comprises performing at least one assay for detecting modulation of a TLR-mediated cellular activity.

The nature of the invention is drawn to a method of identifying a compound by detecting the modulation of a first and second cellular activity mediated by a TLR and identifying the compound that selectively modulates at least one cellular activity and selecting a target modulation profile of cellular activities mediated by a common TLR. The disclosure teaches a method of screening compounds in human embryonic kidney cells and Namalwa cells (human Burkitt's lymphoma cells) for cellular activities mediated by TLR7.

Ten human (Chuang et al., Biochim Biophys Acta. 2001 Mar 19; 1518(1-2):157-61, especially p. 157, column 1, second paragraph to column 2, first paragraph) and twelve murine TLRs are known in the art (see, for example, Kaisho et al., J Allergy Clin Immunol 2006 May;117(5):979-87; Epub 2006 Apr 3, Review; p. 979, second column, first paragraph). It is well known that each TLR is structurally and functionally very different (Kaisho et al., p. 980, Figure 1; p. 984, Figure 4). Nucleic acid TLR ligands are recognized in different cellular compartments from lipid or protein TLR ligands. Lipid or protein TLR ligands are recognized on the plasma membrane, whereas nucleic acids are recognized by TLRs in the endosome. Nucleic acid TLR ligands are also unique among TLR agonists in their ability to induce type I IFNs, including both IFN-α and IFN-β. Lipid or protein TLR ligands fail to induce type I IFNs, although LPS is exceptional in that it can induce IFN-β but not IFN-α (Kaisho et al., p. 982, column 1, second paragraph to column 2, first paragraph). TLR signaling can lead to activation of several transcription factors, including NF-κβ and IRFs (Kaisho et al,. p. 983, second column, last paragraph; p.

984, Figure 4). Each TLR activates similar signaling pathways, but some TLRs trigger specific pathways. This differential induction pattern depends on cytoplasmic adapter molecules, such as MyD88, that can associate with the intracytoplasmic region of TLRs (Kaisho et al., p. 983, second column, last paragraph; p. 984 in its entirety). However, there are characterized MyD88-independent pathways that are used in TLR3 and TLR4 signaling (Kaisho et al., p. 984, second column). See also, Medzhitov et al., (US Patent 6,960,343, 1 November 2005, published as US 2003/0023993 on 30 January 2003, who teach that in mammalian species there are at least ten TLRs and each has a distinct function in innate immune recognition. The TLRs differ from one another with regard to ligand specificity, the use of accessory proteins, expression profiles, and differences in signal transduction pathways (column 1, lines 62-67).

Unlike TLR3 and TLR4, stimulation of TLR7 or TLR9 leads to type I IFN responses through the MyD88 pathway. TLR7 and TLR9 are specifically designed to recognize the nucleoside-based products derived from viruses (Kaisho et al., p. 985, column 1, third paragraph). However, downstream of MyD88, signaling pathways are bifurcated into NF-κβ and IRF-7-activating pathways (Kaisho et al., p. 985, column 1, fourth paragraph; p. 984, Figure 4). Activation of the NF-κβ pathway is required for inflammatory gene expression, but the IRF-7 pathway is essential for type I IFN gene induction (Kaisho et al., p. 985, first column, fourth paragraph). However, "[i]t is still unclear how the molecular complex including MyD88, IRAK-1, and IRF-7 leads to NF-κβ or IRF-7 activation and induction of type I IFN genes" (Kaisho et al., p. 985, fifth paragraph).

The level of skill of those in the art is extremely high due to the multifactorial parameters necessary to determine the combinations and components to be measured in the highly complex TLR signaling pathway. The level of skill is so high, in part, because the nature of the TLR signaling pathway is very complex, utilizing 10 distinct TLRs, at least 5 distinct cytoplasmic adapter molecules, and is still not entirely characterized, making even routine experimentation entirely unpredictable. It is well known in the art, as evidenced by the above-cited references, that the level of predictability involving the TLR-signaling pathway is incredibly high because of the diversity of the TLRs themselves as well as the diversity of cytoplasmic adapter proteins involved in the TLR-signaling pathway.

The specification discloses two working models of using a method for identifying a compound, by detecting modulation of cellular activities mediated by human TLR7 in HEK and Namalwa cells. However, no guidance is provided as to whether the same method will work in different cell types, in different species, or with different TLRs. The disclosure teaches only human TLR7 modulation. Applicants' claims, as written, are excessively broad due, in part, to the complex and diverse nature of the TLR signaling pathway and the number of TLRs and cytoplasmic adapter molecules in different species.

Although candidate compound screening assays are well known in the art, not all cellular activities are known for all TLRs. Because of the significant differences and compounding variables of the different TLRs in different species, the different cytoplasmic adapter proteins, and the numerous signal transduction pathways for TLR-induced cellular activities, some of which are still unknown, candidate compound screening assays on all TLRs (as broadly claimed) from all species is beyond the scope of what is known in the art or taught in the instant specification and would require undue experimentation.

Therefore, based on the discussions above concerning the art's recognition that the diversity of TLRs and associated proteins involved in the TLR signaling pathway, TLR modulation and TLR-induced output in a given cell will be unique and specific because depends on a variety of factors, including the nature of the activating ligand (i.e., protein, nucleic acid, LPS, CpG, etc.), the particular TLR or combination of TLRs, and the various non-overlapping cytoplasmic adapter molecules that are activated in the pathway, the full extent of which has yet to be elucidated. The specification fails to teach the skilled artisan how to use the claimed methods without resorting to undue experimentation to determine which of the numerous TLRs from different species may be modulated by the method. Without knowing the mechanism of TLR induction or the TLR to be induced (i.e. TLR7 modulation by ssRNA induction) modulation of a cellular activity mediated by a particular TLR would be incredibly difficult to identify without undue experimentation.

Due to the large quantity of experimentation necessary to determine which TLR is being modulated, such that it can be determined how to use the claimed method of identifying a compound that modulates at least one cellular activity mediated by a common TLR, the lack of direction/guidance presented in the specification regarding same, the absence of a sufficient number of diverse working examples directed to same, the complex nature of the invention, the state of the prior art establishing that TLR-induced output in a given cell will be unique and specific because it will depend on a number of different factors, and the breadth of the claims which fail to recite particular TLRs or TLR signaling pathways to be targeted by the unknown compounds, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, Second Paragraph

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 1-2, and 5-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are drawn to a method of identifying a compound by detecting the modulation of a first and second cellular activity mediated by a TLR and identifying the compound that selectively modulates at least one cellular activity and selecting a target modulation profile of cellular activities mediated by a common TLR. The terms "at least one cellular activity, " "cellular activity," "first cellular activity," "second cellular activity," and "TLR-mediated cellular activity" fail to limit the thousands of activities of cells, such that the metes and bounds of the term can be ascertained by one of ordinary skill in the art. The terms not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

9. Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "selectively modulates" in claims 1-2 is a relative term which renders the claim indefinite. The term "selectively modulates" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The specification recites only that "selectively modulate" be a non-general activity (specification p. 8, line 15).

10. Claims 1-2 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "different extent" in claim 2 is a relative term which renders the claim indefinite. The term "different extent" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

Claim Rejections - 35 USC § 102

11. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

12. Claims 1-2 and 5-7 are rejected under 35 U.S.C. 102(a) as being anticipated by Medzhitov et al., (US 2003/0023993, published 30 January 2003, now US Patent 6,960,343, 1 November 2005).

The claims recite a method of identifying a compound that selectively modulates at least one cellular activity of a plurality of cellular activities mediated by a common TLR comprising detecting modulation of a first cellular activity mediated by a TLR, detecting modulation of a second cellular activity mediated by the TLR and identifying the test compound as a compound that selectively modulates at least one cellular activity of a plurality of cellular activities mediated by a common TLR if the test compound modulates the first cellular activity to a different extent than it modulates the second cellular activity; wherein the test compound modulates the first cellular activity and does not modulate the second cellular activity; the method comprising selecting a target modulation profile of cellular activities mediated by a common TLR, determining the modulation profile of cellular activities mediated by a common TLR for a test compound and identifying the test compound as a target compound if the modulation profile of the test compound conforms to the target modulation profile; wherein the target modulation profile includes one or more TLR-mediated cellular activities that are not detectably modulated by a target compound; wherein the determining the modulation profile of a test compound comprises performing at least one assay for detecting modulation of a TLR-mediated cellular activity.

US 2003/0023993 teaches a method of identifying a compound which selectively modulates the TLR4 signaling pathway (Example 3, column 24, lines 60-67 to column 25, lines 1-53). Detection of phosphorylated PKR , NFκβ and JNK activation were measured (column 25, lines 13-23). LPS was shown to activate PKR through the MyD88-dependent pathway as well as through a MyD88-independent pathway, with lower kinetics (column 25, lines 18-25). PKR activation was also tested in response to CpG stimulation (column 25, lines 25-54) to determine whether the TIRAP (one of the cytoplasmic adapter proteins) directly or indirectly regulates PKR. The interaction between TIRAP, p58 and PACT were analyzed (column 25, lines 40-67 to column 26, lines 1-62; Examples 3 and 4). LPS activated cells that were pretreated with DMSO or a dominant negative TIRAP did not activate the NF-κβ (column 26, lines 2-20). The TIRAP peptide, but not the control peptide, also inhibited PKR phosphorylation induced by LPS but not CpG, in RAW cells (column 26, lines 49-53). The effect of TIRAP peptide on cytokine

production was also tested . The addition of the TIRAP peptide inhibited production of IL-12 and IL-6 in response to stimulation by LPS, but not CpG (column 27, lines 15-21).

13. Claims 1-2 and 5-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Medzhitov et al., (US Patent 6,960,343, 1 November 2005, benefit to 9 May 2001), hereinafter the '343 patent.

The claims recite a method of identifying a compound that selectively modulates at least one cellular activity of a plurality of cellular activities mediated by a common TLR comprising detecting modulation of a first cellular activity mediated by a TLR, detecting modulation of a second cellular activity mediated by the TLR and identifying the test compound as a compound that selectively modulates at least one cellular activity of a plurality of cellular activities mediated by a common TLR if the test compound modulates the first cellular activity to a different extent than it modulates the second cellular activity; wherein the test compound modulates the first cellular activity and does not modulate the second cellular activity; the method comprising selecting a target modulation profile of cellular activities mediated by a common TLR, determining the modulation profile of cellular activities mediated by a common TLR for a test compound and identifying the test compound as a target compound if the modulation profile of the test compound conforms to the target modulation profile; wherein the target modulation profile includes one or more TLR-mediated cellular activities that are not detectably modulated by a target compound; wherein the determining the modulation profile of a test compound comprises performing at least one assay for detecting modulation of a TLR-mediated cellular activity.

The '343 patent teaches a method of identifying a compound which selectively modulates the TLR4 signaling pathway (Example 3, column 24, lines 60-67 to column 25, lines 1-53). Detection of phosphorylated PKR , NFκβ and JNK activation were measured (column 25, lines 13-23). LPS was shown to activate PKR through the MyD88-dependent pathway as well as through a MyD88-independent pathway, with lower kinetics (column 25, lines 18-25). PKR activation was also tested in response to CpG stimulation (column 25, lines 25-54) to determine whether the TIRAP (one of the cytoplasmic adapter proteins) directly or indirectly regulates PKR. The interaction between TIRAP, p58 and PACT were analyzed (column 25, lines 40-67 to column 26, lines 1-62; Examples 3 and 4). LPS activated cells that were pretreated with DMSO or a dominant negative TIRAP did not activate the NF-κβ (column 26, lines 2-20). The TIRAP peptide, but not the control peptide, also inhibited PKR phosphorylation induced by LPS but not CpG, in RAW cells (column 26, lines 49-53). The effect of TIRAP peptide on cytokine production was also tested . The addition of the TIRAP peptide inhibited production of IL-12 and IL-6 in response to stimulation by LPS, but not CpG (column 27, lines 15-21).

14. Claims 1-2 and 5-7 are rejected under 35 U.S.C. 102(e) as being anticipated by Beutler et al., (US Patent 7,029,861, 18 April 2006, benefit to 15 September 1998), hereinafter the '861 patent.

The claims recite a method of identifying a compound that selectively modulates at least one cellular activity of a plurality of cellular activities mediated by a common TLR comprising detecting modulation of a first cellular activity mediated by a TLR, detecting modulation of a second cellular activity mediated by the TLR and identifying the test compound as a compound that selectively modulates at least one cellular activity of a plurality of cellular activities mediated by a common TLR if the test compound modulates the first cellular activity to a different extent than it modulates the second cellular activity; wherein the test compound modulates the first cellular activity and does not modulate the second cellular activity; the method comprising selecting a target modulation profile of cellular activities mediated by a common TLR, determining the modulation profile of cellular activities mediated by a common TLR for a test compound and identifying the test compound as a target compound if the modulation profile of the test compound conforms to the target modulation profile; wherein the target modulation profile includes one or more TLR-mediated cellular activities that are not detectably modulated by a target compound; wherein the determining the modulation profile of a test compound comprises performing at least one assay for detecting modulation of a TLR-mediated cellular activity.

The '861 patent teaches methods of identifying TLR4 (human) and tlr4 (murine) inhibitory or stimulatory compounds by monitoring the standard activity profile of TLR4 in the presence and absence of the candidate substance and comparing the results (column 45, lines 31-50; see also column 64, lines 51-67 to column 67, line 51). The method includes identification of a test compound that promotes, augments, or increases the activity of TLR4 (column 45, lines 52-59). The method steps to generally include: (i) providing a cell expressing a TLR4 polypeptide; (ii) determining the activity of said TLR4 polypeptide [i.e. first cellular activity]; (iii) contacting said cell with a candidate substance; and (iv) comparing the TLR4 activity of the cell in step iii with the TLR4 activity observed when said candidate substance is not added [i.e. second cellular activity] wherein an alteration in activity indicates that said candidate substance is a modulator of activity (column 45, lines 66-67 to column 46, lines 1-19). The candidate compounds may be a protein, protein fragment, a small molecule, or a nucleic acid (column 46, lines 25-27). Additional screening assay methods, including compounds that achieve significant appropriate changes, are taught at column 46, lines 57-67 to column 47, lines 1-16). Examples, such as LPS response assays and validation are taught in column 56, Example 2, and includes use of an index of

responsiveness, which can be compared to the target modulation profile. Tlr4-mediated signal transduction is taught in Example 9, column 69, lines 29-67 to column 73, line 67.

Conclusion

NO CLAIM IS ALLOWED.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cherie M. Woodward whose telephone number is (571) 272-3329. The examiner can normally be reached on Monday - Thursday 9:00am-7:30pm (EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CMW

CHRISTINE J. SAOUD
PRIMARY EXAMINER
Christine J. Saoud